

Endogenous 3-methylhistidine excretion in healthy women and men with reference to muscle protein metabolism

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Summary

Presently 3-methylhistidine excretion is widely used for monitoring the metabolic status of patients during different kinds of clinical conditions. Aim of the study was to reconsider its predicative value on the basis of a larger collective of healthy persons and to find a standardization independent from sex. Therefore endogenous 3-methylhistidine release of 40 healthy adults (24 women and 16 men) was measured and related to body weight, body surface area, arm muscle circumference, and nitrogen and creatinine excretion. A positive correlation could be observed only for 3-methylhistidine and creatinine excretion and that to the same extent both for females and males. Assuming that the excreted 3-methylhistidine is mainly originating from muscle protein the calculated daily protein breakdown amounted for women 39.9 g and 68.1 g for men. No difference between females and males could be observed in the percentual turnover of myofibrillar protein which has been estimated with 0.90 and 0.98 respectively. We interpret our results saying that endogenous 3-methylhistidine excretion is a valuable indicator for muscle protein breakdown in humans with intact kidney function. For the assessment of muscle proteolysis by 3-methylhistidine excretion in heterogenous groups of patients it is recommended to use the 3-methylhistidine/creatinine ratio or the percental turnover of myofibrillar protein.

Zusammenfassung

Die 3-MHIS-Ausscheidung wird gegenwärtig bei den unterschiedlichsten klinischen Bedingungen als Monitor der Stoffwechsellage der Patienten herangezogen. Ziel dieser Studie war es, die Aussagefähigkeit dieser Meßgröße anhand eines größeren Kollektivs von gesunden Personen zu überprüfen und unabhängig vom Geschlecht standardisieren zu können. Es wurde deshalb von insgesamt 40 gesunden Erwachsenen (24 Frauen und 16 Männern) am 4. Tag einer 3-MHIS-freien Ernährung die endogene 3-MHIS-Freisetzung gemessen und zu Körpergewicht, Körperoberfläche, Armmuskelumfang, Stickstoff- und Creatininausscheidung in Beziehung gesetzt. Eine positive Korrelation ergab sich sowohl bei den Frauen als auch bei den Männern – und zwar im gleichen Ausmaß – nur zwischen der 3-MHIS- und Creatininausscheidung. Falls die Annahme stimmt, daß das ausgeschiedene 3-MHIS hauptsächlich dem Muskelprotein entstammt, beliefe sich die tägliche abgebaute Menge bei den Frauen auf 39,9 g und 68,1 g bei den Männern, der prozentuale TMP wäre in diesem Fall für Frauen und Männer gleich und wurde jeweils mit 0,90 und 0,98 bestimmt. Wir interpretieren unsere Ergebnisse dahingehend, daß die endogene 3-MHIS-Ausscheidung ein realistisches Maß für den Muskelproteinabbau beim Menschen mit intakter Nierenfunktion darstellt. Bei der Beurteilung der Muskelproteolyse anhand der 3-MHIS-Ausscheidung von sehr heterogenen Patientengruppen empfiehlt es sich, die 3-MHIS-Ausscheiderate entweder als 3-MHIS/Cr-Quotient oder als % TMP auszudrücken.

Key words: 3-methylhistidine/creatinine ratio, muscle protein turnover, reference values

Introduction

After the discovery of 3-methylhistidine (3-MHIS) as a constituent of human urine by Tallan, Stein and Moore in 1953 (1) several authors became engaged to throw light on the origin of this substance and to elucidate its significance in metabolism. It was established that 3-MHIS is mainly localized in skeletal muscle (2, 3) where it is formed by post-ribosomal methylation of specific histidine residues (4, 5) in actin of all and in myosin of white fibres (6, 7, 8) and that it is neither reutilized for protein synthesis (9) nor oxidatively metabolized (10) after being released during myofibrillar protein breakdown, but quantitatively excreted in the urine (11, 12). By the exploration of the biochemical background – mainly obtained through rat experiments – the possibility was realized to evaluate muscle protein breakdown by measuring 3-MHIS excretion (13, 14). This resulted in a flood of investigations – in animals and humans as well – which all were dealing with muscle proteolysis under various nutritional, hormonal, and pathological conditions – as measured by 3-MHIS excretion. Considering this fact it is rather amazing that until today only very few efforts have been undertaken to establish normal values, which especially for women are hardly available at all. The few values described in the literature, which are mostly derived from a very small number of individuals (15–25), are exhibiting a considerable variance and are referring almost exclusively on the male sex. We feel it desirable and necessary that a rather large number of healthy persons should furnish the basis of comparison for the evaluation of 3-MHIS excretion of the manifold patient groups investigated. The subject matter of the present study was therefore to examine a greater number of healthy women and men on a 3-MHIS free diet regarding 3-MHIS excretion and to recover possible relationships with the frequently used anthropometric indices for nutritional status like body weight (BW), body surface area (BSA), arm muscle circumference (AMC), and muscle mass. Furthermore, we intended to review the 3-MHIS excretion concerning its informative value on muscle protein metabolism by forming the 3-MHIS/creatinine ratio and by calculating the myofibrillar protein catabolic rate (MPCR) and the percental turnover of myofibrillar protein (% TMP).

Materials and methods

Participants of the study

40 persons, students and institute personal of the Johannes Gutenberg-University in Mainz of which were 24 women with an age ranging from 21 to 56 and 16 men with an age between 22 and 59, were voluntarily participating in this study. All of them were in good health and performing their work as usual.

Experimental design

As it is established by now that 3-MHIS consumed by food will be excreted in urine within 2–3 days (24), the participants were instructed by a nutritionist to eat a 3-MHIS free diet and cover their protein requirements by other sources than 3-MHIS containing proteins, like cheese, eggs, and milk. For determination of 3-MHIS, creatinine (Cr), and nitrogen (N) 24-h urine has been collected on the 4th day. 5 ml of concentrated HCl have been added for preservation and an aliquot has been

stored at -30°C until analysis. Weight and size of all volunteers have been noted on the same day.

Determinations

Analysis of 3-MHIS was performed by ion exchange chromatography on an automatic analyzer by applying a short program, especially developed for this purpose.

The technical details of the sample preparation and the analytical procedure are described in an earlier publication (23). Creatinine was determined kinetically by using a method based on the Jaffé reaction (26). Total nitrogen was recorded by a semi-micromethod applying the Kjeldahl procedure (27).

Skinfold thickness was measured with a Harpenden Caliper in the middle of the upper non-dominant arm over the musculus triceps brachii.

Calculated values: Body surface area has been calculated according to the formula:

$$\text{BSA} = 0.007984 \times \text{height}^{0.725} \times \text{weight}^{0.425}$$

The arm muscle circumference has been calculated by correcting the arm circumference for the subcutaneous fat layer, as measured by the triceps skinfold thickness according to the following formula:

$$\text{Arm muscle circumference (cm)} = \text{arm circumference (cm)} - (0.314 \times \text{triceps skinfold (mm)}) \quad (28).$$

Myofibrillar protein catabolic rate has been derived from the formula according to McKeran et al. (19):

$$\text{MPCR/24 h} = \frac{3\text{-MHIS } (\mu\text{M/24 h})}{5.69}$$

assuming that the 3-MHIS content per g mixed muscle protein is $3.7 \mu\text{M}$ and that the 3-MHIS myofibrillar protein constitutes 65 % of total muscle protein (29). The percental turnover of myofibrillar protein is yielded by relating the MPCR to total myofibrillar muscle protein (TMMP):

$$\% \text{ TMP} = \frac{\text{MPCR g/24 h}}{\text{TMMP (g)}} \times 100$$

It is assumed that protein constitutes 20 % of muscle mass. Muscle mass has been derived from creatinine excretion assuming that 1 g creatinine corresponds to 20 kg muscle mass (30).

Results

The anthropometric description of the participants is subject of table 1 and supplies information on age, weight, size, and calculated body surface area as well as arm muscle circumference and total muscle mass derived from creatinine excretion. All parameters are presented as mean values \pm SEM. Excretion rate of 3-MHIS, creatinine and N, 3-MHIS/Cr and 3-

Table 1. Anthropometric characteristics of the test persons.

		Age (years)	Weight (kg)	Height (cm)	BSA (m^2)	AMC (cm)	Muscle mass (kg)
Women	\bar{x}	27.8	56.6	168.4	1.64	18.7	22.3
(n = 24)	S_E	1.75	1.31	1.02	0.019	0.47	0.92
Men	\bar{x}	32.3	72.5	178.7	1.90	23.8	34.8
(n = 16)	S_E	2.55	2.77	1.96	0.040	0.62	1.10

MHIS/kg BW ratios, as well as calculated myofibrillar catabolic rate and % TMP are listed also as mean values \pm SEM in table 2. The average 3-MHIS excretion for women amounted to $147 \mu\text{M}/24 \text{ h} \pm 7.0$ and yielded only 58.7 % of the mean value of $252 \mu\text{M}/24 \text{ h} \pm 10.3$ for men. The difference between the sexes was similar regarding creatinine excretion: the average daily amount released by women was $1.12 \text{ g} \pm 0.046$ and 1.74 ± 0.054 for males. The results for total urinary N were within the normal range for all persons. Relating 3-MHIS to body weight yielded values of $2.6 \mu\text{M}/\text{kg}/24 \text{ h} \pm 0.62$ for women and $3.5 \mu\text{M}/\text{kg}/\text{day} \pm 0.63$ for men and resulted in a substantial less difference between the two groups: after all the figure for females is coming up to 74.3 % of the one for males. Calculated 3-MHIS/Cr ratios were $133 \mu\text{M} \pm 4.2$ for women and $145 \mu\text{M} \pm 3.8$ for men. In this connexion it has been observed that 3 of the female test persons who were addicted to vegetarianism exhibited a reduced 3-MHIS excretion with values lying 41 % below the average amount for the whole collective, while on the other hand creatinine values were only diminished to 70.5 %.

The same results are also reflected by the calculated MPCR as well as muscle protein turnover. The greatest difference between the sexes is prominent for the absolute MPCR with mean values of $25.9 \text{ g}/24 \text{ h} \pm 1.28$ for females and $44.2 \text{ g}/24 \text{ h} \pm 1.86$ for males. It becomes smaller when relating the MPCR to body weight and nearly disappears for muscle protein turnover, which has been estimated to be 0.9 % for women and 0.98 % for men.

Table 2. Excretion rates of 3-MHIS, creatinine and N; 3-MHIS/Cr and 3-MHIS/kg BW ratios and calculated MPCR, as absolute values and in relation to body weight, as well as % TMP.

		3-MHIS/24 h μM	CR/24 h g	N/24 h g	3-MHIS/Cr $\mu\text{M}/\text{g}$	3-MHIS/kg μM	MPCR/kg g	MPCR abs. g	TMP %
Women	\bar{x}	147.7	1.12	7.84	132.9	2.6	0.46	25.9	0.90
(n = 24)	S_E	6.98	0.046	0.568	4.18	0.62	0.022	1.28	0.028
Men	\bar{x}	251.8	1.74	11.37	144.9	3.5	0.62	44.2	0.98
(n = 16)	S_E	10.27	0.054	0.730	3.78	0.63	0.030	1.86	0.050

The assumption that 1 g of muscle protein corresponds to $3.7 \mu\text{M}$ 3-MHIS allows calculation of the daily degradation of muscle protein which was coming up to $39.9 \text{ g}/24 \text{ h}$ for women and to $68.2 \text{ g}/24 \text{ h}$ for men. Graphical illustration is presented in figura 1. The different levels of absolute excretion rates of 3-MHIS for both sexes and 3-MHIS/Cr and 3-MHIS/kg BW ratios are illustrated in the graphical comparison by means of statistical description of the material in figura 2. No significant correlation could be detected between 3-MHIS and AMC, BSA, BW or N excretion; however, Cr excretion was correlating significantly with 3-MHIS excretion and that both for women ($r = 0.778$) and for men ($r = 0.764$). Figure 3 shows the graphical illustration of the regression lines.

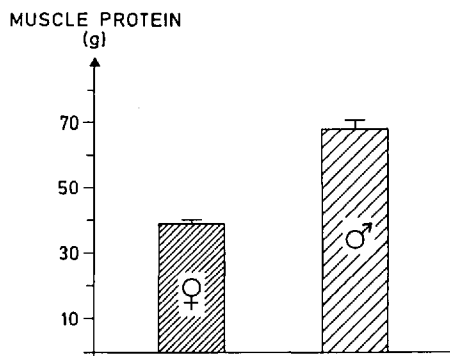


Fig. 1. Daily degraded muscle protein breakdown as calculated by 3-MHIS excretion.

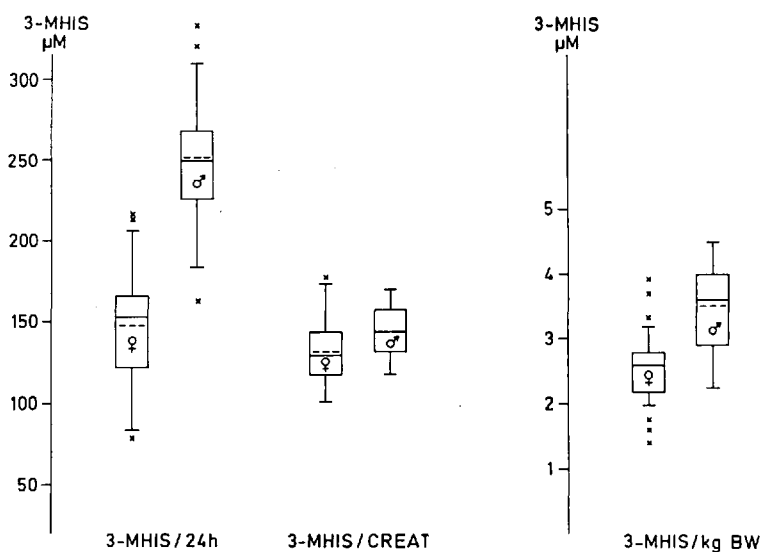


Fig. 2. Statistical description (----- mean, ——— median, box = quartile deviation, ——— dispersion, and x = extreme values) of the different levels of absolute excretion rates of 3-MHIS, and of 3-MHIS/Cr and 3-MHIS/kg BW ratios comparing women and men.

Discussion

Today it is generally acknowledged that 3-MHIS excretion may supply a measure for protein breakdown and is widely used to record the progress of diseases associated with metabolic disorders. Usually the investigated patient groups are rather small and heterogeneous and only very seldom

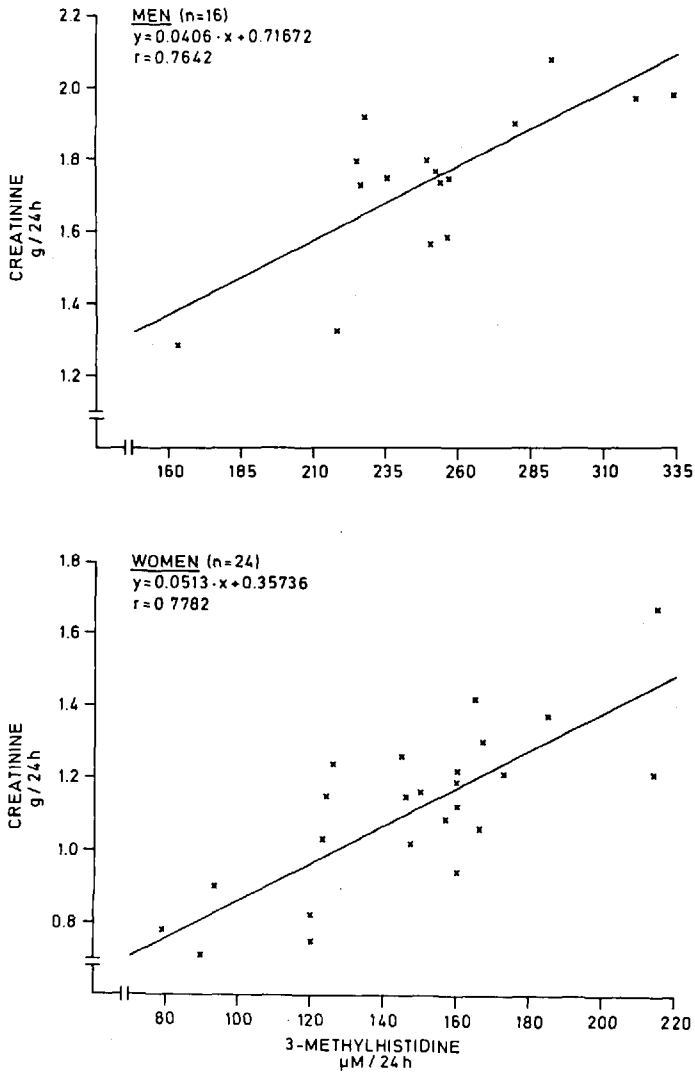


Fig. 3. Graphical illustration of regression analyses showing the relationship between 3-MHIS and Cr excretion for men and women.

one has the chance to obtain control data before the onset of a disease of a patient. A prerequisite for using 3-MHIS excretion as monitor of abnormal conditions are therefore standardized normal values. Until now greater groups of healthy persons have been examined regarding 3-MHIS excretion only by Lukaski and Mendez (24, 25), Neuhäuser and Fürst (23) and in a study by Long (17). The own study was referring to persons not imposed on any dietary restriction and furnished an overview on 3-MHIS excretion

during an average food consumption. For estimation and comparisons of absolute endogenous 3-MHIS excretion however, a 3-MHIS free diet is necessary (20, 24).

Average absolute values of healthy persons as stated in the literature are ranging from 203–280 μM for men and from 75–210 μM for women (15–25). Our mean values are nearly exactly lying in the middle of those figures indicating a rather representative collective. Assuming that 3-MHIS excretion is reflecting muscle protein breakdown means that absolute values are depending on muscle mass which limits the predicative value when comparing groups consisting of very different individuals. With this background one is trying to reduce 3-MHIS excretion to a common denominator.

We could not detect any age-dependent interrelation for 3-MHIS excretion in the persons investigated (19–59 years). Young et al. (18) observed a decreased 3-MHIS excretion in six 77-year-old women which he explained by reduced muscle mass. Tomas et al. (21) investigated age-related changes of myofibrillar protein catabolic rate by 3-MHIS and Cr excretion and observed a considerable decline of 3-MHIS/Cr ratio from birth to maturity and a stabilization from then on which is in accordance with our results. For better comparison it is a common habit to relate 3-MHIS excretion to body weight and use the 3-MHIS/kg ratio which will result in a diminution of the sex specific difference – as shown also by our results. This should, however, not obscure the fact that no correlation is existing between 3-MHIS excretion and body weight, when evaluating men and women separately. No correlation could be detected between either BSA or N excretion. According to the classical representations by Kleiber (30) basic metabolic rate is proportional to BSA – which might promote the speculation that under healthy conditions muscle protein breakdown is running off independently from basic metabolic rate or total protein metabolism. The latter conclusion would differ from observations in traumatic conditions where either positive or negative correlations between N and 3-MHIS have been demonstrated (31).

According to Blackburn et al. (28) the measurement of the AMC is a simple and precise method for assessing muscle mass and thus nutritional status. Our data do not reveal any correlation between AMC and 3-MHIS excretion for women and only a weak correlation ($r = 0.591$) for men. It is likely that AMC alone is not a sufficient reflector of muscle mass and that skinfold thickness must be measured at several points (biceps, triceps, subscapular, and suprailiac) (32, 33, 34) to enable exact statements of fatfree body mass and thus muscle mass.

Creatinine excretion today is commonly used as indicator for muscle mass equating 1 g of creatinine with 20 kg of muscle mass. The distinct correlations between 3-MHIS and Cr excretion which are equal for men and women support the opinion that 3-MHIS is mainly originating from skeletal muscle against the view it might be generated also in substantial amounts from other tissues with higher turnover rates like the intestinal tract or skin (35, 36, 37). Values for 3-MHIS/Cr ratio – as reported in the literature – are ranging from 93 to 152 μM 3-MHIS/g Cr. Our data coincide best with the figure from Lukaski et al. (138 μM 3-MHIS/g Cr) who is the only one who investigated a bigger collective consisting of 16 healthy

males. As there is no statistical difference between the 3-MHIS/Cr ratio of women and men we feel it preferable to use this index when investigating mixed collectives. 3-MHIS content per muscle protein is defined by different values and is ranging from $3.2 \mu\text{M}$ (2) and $3.63 \mu\text{M}$ (21) to $4.2 \mu\text{M}$ (38). We were using the mean of these statements when calculating the myofibrillar catabolic rate according to Halliday. Average MPCr has been reevaluated from normal values available in the literature (39) and calculated to be $0.47 \text{ g} \pm 0.04$ on the basis that 3-MHIS constitutes $4.2 \mu\text{M}$ per g muscle protein which may explain that our values for the MPCr ($0.46 \text{ g} \pm 0.02$ for females and $0.62 \text{ g} \pm$ for males) are somewhat higher.

MPCR related to body weight is not more favourable for the investigation of mixed collectives than the rates of absolute 3-MHIS excretion and body weight: the average MPCr/kg for males is still 25 % higher than for females. Analogous to the 3-MHIS/Cr ratio, the % TMP is the preferred characteristic relating the daily myofibrillar breakdown to total stock of myofibrillar protein. Values of 0.90 ± 0.028 for women and 0.98 ± 0.050 for men are nearly identical. In this coherence we interpret the reduced 3-MHIS excretion of the 3 female vegetarians as the result of a diminished muscle protein turnover under vegetarian food consumption. Comparing our values for the % TMP with those recalculated from the literature (39) – comprised in the mean value of 0.94 ± 0.07 – shows a remarkable conformity and gives rise to the assumption that the % TMP is independent from sex and nearly constant in the healthy adult.

Absolute average muscle protein breakdown has been estimated with $50 \text{ g}/24 \text{ h}$ (38). Our mean value for muscle protein breakdown of the combined collective, derived from 3-MHIS excretion amounted to 54 g which is lying very close in this range and promotes also our view that 3-MHIS excretion – under the prerequisite of intact kidney function – is yielded a valuable index for statements on muscle protein metabolism.

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